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09/763,362	04/23/2001	Kazuma Tomizuka	081356/0158	4670

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Foley & Lardner
Washington Harbour
Suite 500
3000 K Street NW
Washington, DC 20007-5109

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,362	TOMIZUKA ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/30/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-83,85 and 93-143* is/are pending in the application.

4a) Of the above claim(s) *26-83 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-143* is/are rejected.

7)☒ Claim(s) *93 and 113* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 12/30/03, has been entered.

Claims 26-83, 85, 93-143 are pending. Claims 26-83 and 85 are withdrawn from further consideration as being directed to non-elected groups, Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 93-143 are under current examination.

Claim Objections

Claims 93 and 113 re objected to because of the following informalities: the claims have two step (iv)s. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93-126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of a recombinant chromosome comprising the centromere of human chromosome #14, two telomere sequences, at least one recognition sequence for a site-directed recombination enzyme, at least two chromosome fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment; and a marker gene, wherein the recognition sequence for a site-directed recombination enzyme is located between the two chromosome fragments.

The specification teaches working examples, wherein the human chromosome 14 fragment, SC20, is used to produce the recombinant chromosome of the instant invention, and is retained in almost 100% when introduced into mice, and can be transmitted to its progeny. See p. 63 and 65-66, bridging ¶. The specification teaches that SC20 is obtained by the spontaneous fragmentation of human chromosome 14 by irradiation after microcell-fusion. Particularly, the specification teaches the isolation of spontaneously fragmented human chromosome 14 fragments to identify the fragment which contains the human heavy chain antibody gene. The genomic DNA was prepared from the clones and subjected to PCR analysis and SC20 was identified as containing the antibody heavy chain gene. The fragment was then subjected to FISH analysis. It was confirmed that this fragment also contained a human chromosome 14-derived centromere sequence. This fragment was then used in the working examples of the specification. See Example 68.

The specification teaches the generation of fragments of human chromosome 2 and 22 by the same methodology as for the isolation of the SC20 fragment. The specification teaches that a particular fragment, W23, from human chromosome #2 produced a complete functional human antibody κ chain. See Example 13 and 28. The specification further teaches that a particular cell clone (6-1) containing a particular fragment of chromosome 22, was used to produce chimeric mice expressing the human λ chain in their sera. See Examples 30-34. The specification teaches that the 6-1 clone was obtained by the microcell fusion of mouse A9 cells and human fibroblast HFL-1 cells, and the subsequent irradiation of the fused cells. The specification further teaches the isolation of the 6-1 clone containing the chromosome 22 fragment. See Examples 1-3.

As the SC20, W23 fragments and the 6-1 clone are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the SC20, W23 fragments and the 6-1 clone are not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of SC20, W23 fragments and the 6-1 clone. The specification does not disclose a repeatable process to obtain the SC20, W23 fragments and the 6-1 clone because it teaches the generation of the fragment by spontaneous fragmentation by irradiation, and it is not apparent if it is readily available to the public. If Applicants feel that the production of SC20, W23 fragments and the 6-1 clone is disclosed by a repeatable

process, Applicants are invited to point to specific support in the specification by page and line number.

If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the SC20, W23 fragments and the 6-1 clone have been deposited under the Budapest Treaty and that the SC20, W23 fragments and the 6-1 clone will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

Once the deposit has been perfected, the claims will be limited to the SC20 and W23 fragments and the 6-1 clone.

The specification teaches that it was previously thought that human chromosomes introduced into mice could not be transmitted to the mouse's progeny because of the presence of an abnormal chromosome. However, the specification teaches that a particular fragment, SC20, of the human chromosome which is used in the examples in the specification can be transmitted to progeny. The specification further teaches that there a need in the art to develop techniques that enable the cleaving of human chromosomes at particular points, and not randomly. See pp. 62-63 of the instant specification. The specification further teaches the isolation of chromosome 2 and 22 fragments (W23 and fragment from the 6-1 clone, respectively) which are then used in combination with the SC20 fragment to produce a recombinant chromosome which is capable of producing human antibodies. The specification teaches that the fragments encoding the SC20, W23 and 6-1 clone are produced by microcell-mediated fusion, the subsequent irradiation

and then isolation of the fragments. These methods clearly produce the fragments by spontaneous fragmentation.

The breadth of the claims is not enabling because the specification fails to provide sufficient teachings or guidance with regard to other chromosome fragments, other than the exemplified chromosome #2 and #22 fragments, which comprises a human antibody light-chain kappa gene locus, and a human light chain λ gene locus, respectively. The specification teaches that the recombinant chromosomes of the instant invention would be used to produce mice with human genes, particularly, human genes that encode for antibodies. See p. 5, for example. However, the specification fails to provide guidance with regard to the generation of recombinant chromosomes that have any two chromosomal fragments which do not encode antibody gene loci, and one of skill in the art would not know how to use such a recombinant chromosome. The breadth of the claim encompasses combinations of two proteins which do not function together, for example, an antibody locus and the amylase locus. Further embodiments of the claims limit the chromosome 14 fragment SC20 to a centromere-comprising portion and a *fragment of a chromosome other than human chromosome 14* [see claim 106, for example]. Note that SC20 is taught by the instant specification to contain the human antibody heavy-chain locus and the chromosome 14 centromere. [See Example 68]. Thus, one of skill in the art would not know how to use a recombinant chromosome that contained the SC20 fragment and any particular other chromosome fragment, other

than the exemplified W23 and fragment from the 6-1 clone because the specification fails to provide guidance for such recombinant chromosomes.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the production of recombinant chromosomes have any two chromosome fragments, other than the exemplified chromosome 14, 2 and 22 fragments [SC20, W23 and fragment 6-1 clone], it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claims 127-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The claims are directed to chromosome vectors comprising the centromere of human chromosome 21 and methods of producing the chromosome vectors. The specification fails to describe a fragment of human chromosome 21 and chromosme vectors comprising such a fragment with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described the claims require essential or critical elements that are not adequately described by the specification and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as is relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pffaf v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed chromosome 21 fragment comprising a centromere lacks a written description. The specification fails to describe this fragment and the skilled artisan could not envision the detailed chemical structure for example, the sequence of the claimed fragment, or working examples to show the particular chromosome location and the presence of a centromere within the fragment. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and a potential method of isolating and

using it. The specification fails to provide this description, as it only states that the fragment was screened and used in chimeric mice, and fails to provide a specific description of the chromosome 21 fragment. See pp. 66. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). If Applicants feel that description of this fragment is provided by the instant specification, Applicants are invited to point to a particular page and line number.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claims 127-143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification teaches the spontaneous generation of a human chromosome 21 fragment screened from a monochromosomal hybrid cell library that was stable in a chimeric mouse, and thus, this fragment could be used in the methods taught by the specification for the SC20 (chromosome 14) fragment. See pp. 66-67, bridging ¶. This is not found to be enabling because the state of the art of producing artificial chromosome is such that without specific guidance provided by the specification, one of skill in the art would not be able to make a chromosome 21 fragment comprising a centromere, recombinant chromosomes comprising this fragment and methods of making the same. This is because the state of the art of generation artificial chromosomes is unpredictable, and relies on spontaneous fragmentation of chromosomes to identify desired chromosome fragments. This is supported by the instant specification which teaches that there a need in the art to develop techniques that enable the cleaving of human chromosomes at particular points, and not randomly. See pp. 62-63 of the instant specification. However, the specification fails to provide specific teachings with regard to the generation of the claimed chromosome 21 fragment, wherein the fragment has a centromere, and one of skill in the art would not be able to rely upon the teachings of the art for the generation of a particular fragment, as claimed. For example, the specification fails to provide teachings or guidance with regard to the particular isolation of the fragment, the sequence of the claimed fragment or methods of how such a fragment would be produced, or working examples with regard to chimeric mice comprising

this fragment, or guidance, teachings or evidence that such a fragment would contain a centromere sequence, as required by the claims. The specification merely suggests that such a fragment exists, but does not teach the specific production of the fragment, and one of skill in the art would not be able to rely upon the state of the art of artificial chromosome engineering, because the art relies upon methodologies that produce random fragments of chromosomes.

Accordingly, in view of the lack of teachings or specific guidance by the specification with regard to the production and use of the claimed recombinant chromosome comprising a chromosome 21 fragment, wherein the chromosome fragment has a centromere, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 93 is unclear. The claim recites that the at least two chromosome fragments that "had not been" adjacently located in a natural chromosome ... in part (iv) of the claim. This is unclear because "had not been" does not provide an indication of where the two fragments are with relation to each other. For example,

the two chromosomal fragments could still not be adjacent to each other (i.e., they have not changed in position). Claims 94-112 depend from claim 93.

Claim 94 is unclear. The claim recites that that the recombinant chromosome comprises at least one chromosome fragment that is not naturally located adjacent to the human chromosome #14 fragment. This encompasses portions of chromosome #14 fragments that are distal to each other. For example, is the chromosome fragment that is not naturally located adjacent to the human chromosome #14 fragment from another chromosome? Appropriate correction/amendment is required.

Claim 95 is unclear. The claim recites that the fragment is "a centromere-comprising portion" of the fragment denoted as SC20. This is unclear if there are more than one centromere comprising portions of SC20. Appropriate correction or amendment is required.

Claim 98 as written is unclear. The claim recites that the recombinant chromosome comprises a chromosome 14 and 2 fragment. There is no reference to whether these fragments are the same fragments recited in part (iv) of claim 93. If Applicants wish for the claim to recite that the two fragments recited in claim 98 are the same as the fragments in part (iv) of claim 93, it would be remedial to recite, "wherein the at least two chromosome fragments comprise ...". Claims 99-100 depend from claim 98.

Claim 101 is unclear. The claim recites that the recombinant chromosome comprises a chromosome 14 and 22 fragment. There is no reference in the claim to whether these fragments are the same fragments recited in part (iv) of claim 93. . If Applicants wish for the claim to recite that the two fragments recited in claim 98 are the same as the fragments in part (iv) of claim 93, it would be remedial to recite, "wherein the at least two chromosome fragments comprise ...". Claims 102-103 depend from claim 101.

Claim 113 is unclear. The claim recites that the at least two chromosome fragments that "had not been" adjacently located in a natural chromosome ... in part (iv) of the claim. This is unclear because "had not been" does not provide an indication of where the two fragments are with relation to each other. For example, the two chromosomal fragments could continue not be adjacent to each other. Claims 114-116 depend from claim 113.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 93 is rejected under 35 U.S.C. 102(b) as being anticipated by Tomizuka *et al.* [Nat. Gen., 16:133-143, 1997, **cited in prior Office actions**].

Tomizuka teach the introduction of human chromosome or chromosome fragments into mouse ES cells by microcell-mediated chromosome transfer [MMCT]. In particular, Tomizuka teach the introduction of chromosomes (or chromosome derived fragments) which carry the genes for human antibodies from unrearranged human Ig genes [Ig heavy, λ or κ genes], which are found on human chromosomes 2, 14 and 22, into mouse ES cells. In particular, whole cell fusion of human primary fibroblasts with mouse A9 ES cells was performed, and the resulting hybrid cells were screened by PCR and FISH [see p. 133-134 and Figure 1]. Cells were selected by G418 or puromycin drug resistance [see p. 134, col 1-2, bridging paragraph]. It was found that intact human chromosomes 14 and 22 were identified in hybrids A9/14-C11 and A9/22-G2. Tomizuka teach using the Cre-loxP system to replace specific mouse chromosomal regions with the corresponding human chromosomal fragment in the microcell-hybrid ES cells by homologous recombination [see p. 140, 2nd column, 2nd full paragraph, lines 4-7].

Note that Tomizuka teach the limitation of the claims with regard to a targeting vector containing a "telomere sequence" because they teach that intact human chromosomes were identified in the microcell-hybrid ES cells, and intact human chromosomes would have a telomere sequence. Furthermore, the cited art anticipates the claim because the recitation of, "chromosomal fragments that had not been adjacently located in a natural chromosome or in a naturally occurring chromosome fragment" in part (iv) of the claim encompasses parts of the naturally

occurring chromosome 14 that are distal to each other. These chromosomal portions would not be considered to be "adjacent" to each other, because the term "adjacent" is defined as "not distant". For example, two portions of a chromosome where a loxP site had been inserted between that were originally distal to each other would continue to be distal to each other. Thus, this meets the limitation of the claim. Furthermore, with regard to the limitation of a recognition sequence for a site-directed recombination enzyme (part iii), Applicants have previously argued that Tomizuka employs the Cre-loxP system to remove a marker gene, and not to join together separate chromosome fragments. This is not persuasive because the claim reads on an entire chromosome with a loxP insertion.

Accordingly, Tomizuka *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT
Thaian N. Ton
Patent Examiner
Group 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630